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Left Atrial Injection of Protamine Does Not Reliably Prevent Pulmonary Hypertension

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Pulmonary hypertension (PHT) and systemic hypotension following protamine administration of heparin have been well described in animals and humans.[1] Left atrial (LA) or aortic injection of protamine has been advocated as a means of preventing these adverse hemodynamic responses. Two of the following three cases show differing responses to left-sided injection of protamine following right atrial injection. A third case resulted in PHT following an initial LA injection. We suggest that LA or aortic administration of protamine may occasionally be beneficial, but that it certainly does not reliably prevent PHT from protamine in all cases.

CASE REPORTS

Case 1. A 71-yr-old, 70-kg woman with coronary artery disease and increasing angina was scheduled for coronary artery bypass grafting. One month prior to surgery, she had an anterolateral myocardial infarction. There was no history of PHT, diabetes mellitus, or fish allergies. Preoperative physical examination and laboratory studies were normal except for evidence of the previous infarction. Her medications included diltiazem 30 mg q6h and isordil 20 mg q6h po.

Premedication included morphine sulfate 6 mg im and lorazepam 2 mg po. Initial hemodynamic values, prior to induction of anesthesia, were pulmonary artery pressure (PAP) 25/12 mmHg, pulmonary capillary wedge (PCW) 8 mmHg, central venous pressure (CVP) 8 mmHg, and cardiac output (CO) 2.5 l/min.

Anesthesia was achieved by iv fentanyl and diazepam and paralysis with iv pancuronium and metocurine. Prior to CPB, 4 mg/kg of beef lung heparin was given iv. The placement of three vein grafts required a cardiopulmonary bypass (CPB) time of 175 min with an aortic cross-clamp time of 84 min. Separation from CPB was accomplished easily without the aid of inotropic drugs or vasopressors. Hemodynamics after separation were arterial blood pressure (BP) 140/50 mmHg, heart rate (HR) 85 bpm, PAP 18/8 mmHg, CVP 5 mmHg, and CO 3.5 l/min. After the administration of protamine, 30 mg over 2 min *via* the CVP line, the PAP rose to 42/20 mmHg with an associated decrease in BP to 40 mmHg systolic. The right ventricle became visibly distended with a noticeable decrease in contractility. Calcium chloride 1 gram was administered iv and an epinephrine infusion at 4 μg/min was started, with return of hemodynamics to baseline. The remainder of the protamine, 180 mg, was administered *via* the LA line over approximately 15 min without untoward hemodynamic sequelae. The remainder of the operation was uneventful.

Case 2. A 67-yr-old, 70-kg man was scheduled for aortic valve replacement for aortic stenosis. His past medical history was significant for increasing dyspnea on exertion and exertional chest pain over the past 2 yr. The patient's history was negative for PHT, diabetes mellitus, or allergies to fish. Cardiac catheterization revealed a 75 mmHg left ventrical to aortic pressure gradient, normal coronary artery anatomy, and normal pulmonary artery pressures. Medications included propranolol 10 mg BID and diltiazem 20 mg q6h.

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Premedication was with morphine sulfate 5 mg im and scopolamine 0.4 mg im. Hemodynamic values after the placement of vascular cannulae prior to induction were PAP 28/10 mmHg, PCW 8 mmHg, CVP 6 mmHg, and CO 5 l/min. Anesthesia was induced with thiopental iv, sufentanil iv, and maintained with incremental sufentanil iv, and inhalation of enflurane. Pancuronium iv was used for muscle relaxation.

Prior to CPB, the patient received beef lung heparin 4 mg/kg iv. The patient was weaned from CPB with epinephrine 2 μg/min and dobutamine 500 μg/min with BP 120/80 mmHg and CO 5.5 l/min in normal sinus rhythm. Approximately 5 min after CPB, protamine administration was initiated *via* the CVP line. At this time, the PAP was 30/10 mmHg. After 10 mg of protamine was given iv over approximately 2 min, the PAP increased to 60/20 mmHg and arterial BP fell to 80/50 mmHg. The right heart distended with less vigorous contraction. Calcium chloride 1 gram and epinephrine 4 μg/min were given iv with a return of hemodynamics to baseline. The remaining 170 mg of protamine was given directly into the aorta in 10-mg increments. Pulmonary hypertension and systemic hypotension occured following each dose of protamine. Using an increasing epinephrine infusion to maintain hemodynamics, all the heparin was reversed with protamine. The activated clotting time (ACT) returned to normal; the epinephrine was weaned and the patient's subsequent postoperative course was uneventful.

Case 3. A 58-yr-old 65-kg man with coronary artery disease was scheduled for coronary artery bypass grafting. His medical history included a myocardial infarction 9 months prior to admission, increasing chest pain, insulin dependent diabetes mellitus, hypercholesterolemia, and a 20 pack/yr smoking history. Cardiac catheterization demonstrated triple vessel disease, anterolateral hypokineses, and apical dyskinesis. Medication included NPH insulin 45 units and regular insulin 62 units every AM, transderm nitroglycerin 5 mg daily, and nifedipine 10 mg TID. The patient had a history of an allergic reaction to a previously used insulin preparation resulting in acute swelling at the injection site. There was no history of PHT or fish allergies. Physical examination and laboratory tests were normal except for the electrocardiogram, which showed Q waves in V_2 and V_5.

The patient was premedicated with morphine sulfate 6 mg im and lorazepam 2 mg po. Prior to induction of anesthesia, PAP was 23/11 mmHg, CVP 6 mmHg, and CO was 4.9 l/min. Arterial blood gases and electrolytes were within normal limits. Anesthesia was induced with fentanyl, thiamylal, and diazepam iv. Muscle relaxation was obtained with iv pancuronium and metocurine. Anesthesia was maintained by inhalation of fentanyl and enflurane. Beef lung heparin 4 mg/kg was administered prior to cannulation and CPB. Separation from CPB required epinephrine at 2 μg/min for 5 min. At 10 min post-CPB, with good hemodynamic stability without inotropes, protamine was injected into the LA line. An initial dose of 50 mg was given iv over approximately 1–2 min. With this, the PAP rose from 20/8 to 40/18 mmHg, with an associated drop in the arterial BP from 100/70 to 70/40 mmHg. The right ventricle became noticeably distended with decreased contractility. Heart rate increased slightly from 90 to 100 bpm. Hemodynamic stability was restored with calcium chloride 1 gram iv and an iv epinephrine infusion at 2 μg/min. Another 150 mg of protamine was subsuquently administered *via* the LA line over 10 min with another increase in PAP requiring an epinephrine drip of 3–4 μg/min.

The remainder of the operative course was uneventful. The patient arrived in the recovery room without inotropes and with stable hemodynamics, and did well.

Discussion

A spectrum of adverse hemodynamic responses, including PHT, systemic vasodilation, and impaired myocardial contractility, have been reported in animals and humans following protamine reversal of heparin.[1] A variety of interventions to prevent these reactions have been proposed, including iv crystalloid administration prior to protamine, slow rate of protamine infusion, concomitant use of inotropic drugs and injection into the left side of the circulation.[2–4] These suggestions are largely empiric, since the mechanisms responsible for altered hemodynamics are incompletely understood.

In patient 1, the LA injection of protamine was without adverse hemodynamic sequelae after the initial right atrial injection resulted in PHT and systemic hypotension. PHT occurred after both the initial right and subsequent left atrial injection in patient 2. Patient 3 experienced similar PHT when the protamine was administered solely through the LA line.

LA injection of protamine was initially recommended by Aris *et al.* to prevent protamine-induced hypotension.[4] Earlier work examining pulmonary hemodynamic responses to protamine is conflicting. Lowenstein *et al.* reported, in anecdotal fashion, catastrophic pulmonary vasoconstriction following LA injection of protamine.[5] Studies in pigs demonstrated PHT and decreased CO when protamine was given either intravenously or directly into the aorta.[6] In a clinical study, ten patients showed no significant changes in PAP, pulmonary vascular resistance (PVR), or CO with either route of injection.[7] Another human study, however, showed significant decreases in BP and systemic vascular resistance (SVR) only from right atrial injections.[8]

It is likely that PHT associated with protamine administration is caused by release of vasoactive substances, rather than from direct cardiac or vascular effects of protamine or protamine-heparin complexes. Morel *et al.* recently reported an increase in the complement C5a, as well as the eicosanoid thromboxane B_2 in patients who developed pulmonary hypertension following protamine.[9] In animals, thromboxane release (due to endotoxin or thrombin) results in pulmonary hypertension similar to that observed in our cases.[10] During such a reaction, activation of C5a occurs.[11] *In vitro* work has shown that C5a is activated only during the formation of protamine-heparin complexes, but not when preformed protamine-heparin complexes are added to serum.[12] That is, preformed protamine-heparin complexes do not activate C5a and thromboxane. Since the majority of thromboxane is released from the lung, it is reasonable to speculate that PHT may be prevented by injecting protamine distal to the pulmonary circulation (into the LA or aorta), so that only inactive preformed complexes will be "seen" by the lung.

Evidence to support true allergic reactions to protamine resulting in PHT has also been reported. With

allergic reactions, the formation of antigen antibody complexes classically involves IgE, but may also involve IgG or IgM.[13] These complexes, once formed, cause mast cell (or basophil) degranulation or complement activation, and can result in the hemodynamic responses we witnessed.[13] Elevated levels of IgE and IgG associated with adverse hemodynamic effects to protamine have been reported in patients with allergies to protamine zinc insulin and fish, and in male patients with prior vasectomies.[14-18] If PHT resulted from an allergic reaction, the site of injection would make little difference. Unfortunately, in the cases we reported, antibody titers or vasoactive substance levels were not measured.

These data and our cases suggest that pharmacologic blockade of synthesis or action of the vasoactive substances might be more effective in preventing PHT, rather than merely altering the site of injection. Thromboxane synthesis can be abolished by cyclooxygenase inhibitors, such as indomethacin and ibuprofen, or by the specific thromboxane inhibitor dazoxiben.[10] Additionally, thromboxane appears to induce vasoconstriction by increasing calcium influx into the cell.[19] Calcium influx is believed to activate calmodulin, a polypeptide responsible for regulation of myosin light chain kinase resulting in smooth muscle contraction. Thromboxane-induced vasoconstriction might, therefore, be prevented or mitigated by reducing extracellular calcium, blocking slow calcium channels, or inhibiting calmodulin.[19] These interventions are interesting, but are only of potential value at this time. Severe protamine reactions are rare, probably occuring in less than 2% of all cases.[5] This low incidence of adverse reactions, our current inability to predict who will suffer PHT, and the lack of a clearly defined mechanism for the reaction significantly diminishes any practical application of these measures. It should also be remembered that risks and complications could result from the preventive measures suggested. As the mechanism of protamine-induced hypotension is clarified, the use of some of these interventions may eventually become practical.

In conclusion, our cases show that left atrial or aortic administration of protamine to reverse heparin does not reliably prevent PHT. There is some evidence to suggest that different initiating mechanisms may be responsible for the release of the vasoactive substances which cause the PHT response. It is possible, therefore, that some adverse reactions may be prevented or mitigated by left-sided administration of protamine. If this approach is attempted, the potential risk of injecting air or particulate matter into the systemic circulation must be appreciated.

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